20 Dec. 1999

MEMORANDUM FOR NASA HQ/EM
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Washington DC 20546
ATTN: Michael Green

FROM: AFRL/HEST
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SUBJECT: Consultative Letter, AFRL-HE-WP-CL-1999-0032, Summary of Human Kinetic Data on Perchlorate

1. The Air Force Research Laboratory, Human Effectiveness Directorate, Operational Toxicology Branch is researching kinetic studies on humans, using perchlorate and/or iodide, and is developing human physiologically-based pharmacokinetic (PBPK) models. Assistance was provided by Elaine Merrill and Teri Sterner of Operational Technologies Corporation (OpTech), under the Project Management of Dr. Pete Lurker, 1370 North Fairfield Road, Suite A, Beavercreek OH 45432. Ms Merrill was the author of the attachments and is developing the human PBPK model under the technical guidance of Jeff Fisher, PhD (AFRL/HEST). The work was completed under U.S. Air Force Contract DAHA90-06-D-0014. Funding for perchlorate studies was provided in part by NASA HQ/EM, with Michael Green serving as the point of contact. The literature and human PBPK modeling information compiled will be used in the development of an RfD for perchlorate

2. Perchlorate (ClO_4^-) is a groundwater contaminant identified in several states. Perchlorate is not metabolized and is almost completely excreted; however, while in the body perchlorate ions competitively inhibits iodide uptake in the thyroid. Due to these properties, perchlorate is used therapeutically, as a single dose, for iodide discharge tests and as a prophylaxis for occupational radioiodine exposures. Effects of chronic exposures to ClO_4^- (as would be the case with drinking water contamination) are unknown. Hypothetically, if the frequency of exposures does not allow thyroid recovery, in terms of normal iodide uptake and concentration, deficiencies in thyroid hormone production (hypothyroidism) may occur. Iodide is absolutely necessary for production of thyroid hormones. The literature collected and the human PBPK models will be used in the development of an RfD for perchlorate

3. A human physiologically-based pharmacokinetic (PBPK) model to predict the inhibition of thyroid iodine uptake and effect on thyroid hormones is under construction. The preliminary modeling information, presented here, describes physiological parameters involved in systemic clearance of iodide and perchlorate and simultaneous concentrations in the blood, slowly perfused tissue, rapidly perfused tissue, gut, salivary glands and thyroid (Attachment I). The gut,

salivary glands and thyroid compartments are comprised of two compartments to describe non-linear uptake of perchlorate. The blood compartment is also split to describe diffusion from plasma to red blood cells (RBCs). Tissue/blood partition coefficient values were derived from published animal studies. Physiological parameters, affinity constants and kinetic data were obtained from human studies. Systemic clearance of perchlorate was established by fitting limited published human urinary excretion data. Loss and recycling of iodide due to hormone production have not been included at this time, but thyroid hormones models are also under development. Human studies are ongoing, which will provide data for further model development. Ultimately these models will be combined to simulate chronic inhibition of thyroidal iodide uptake by perchlorate over time and the resulting effect on thyroid hormones production.

4. Searches for time course data on perchlorate, or similarly acting ions such as iodide, pertechnetate or nitrate, were performed in several databases including Medline and Toxline (National Library of Medicine), and UnCover. Pertinent journal articles and reports were obtained and additional data sources were identified within the references of those articles. Brief descriptions of relevent studies, from which human time course data were digitized and compile for fitting uptake and elimination constants, are provided in Attachment II. Attachment II is not inclusive of all the studies used in this effort.

David R. Mattie

for Stephen Channel, Lt Col
Chief, Operational Toxicology Branch
Human Effectiveness Directorate

Attachments:
1. Development of Iodide and Perchlorate Models
2. Perchlorate Studies Used for Kinetics Data

cc:
David Mattie, PhD, AFRL/HEST
Pete Lurker, PhD, OpTech Corp.
Annie Jarabek, EPA/NCEA

Attachment I
Development of Iodide and Perchlorate Models

Iodide and Perchlorate Distribution in the Body

The distribution of iodide has been studied on different species. Tables 1 through 4 list organ to blood ratios of various tissues collected from animals dosed with either iodide and/or perchlorate. High concentrations of iodide and perchlorate have been noted in the thyroid, adrenal glands, bile, spleen, gastric mucosa, salivary glands, ovaries, testes, and kidneys. These data were useful in selecting physiological compartments for modeling. These data, however, could not be used for developing partitioning coefficients because the studies did not involve infusions, where the anion concentrations were allowed to reach equilibrium. Due to the rapid elimination of perchlorate and iodide, tissues may have been collected at times when a particular tissue concentration was at a maximum or when most of the anion had been eliminated through urinary excretion.

Table 1 Iodide Organ to Blood Ratios in Rabbits

Rabbits dosed subcutaneously with isotonic solution of NaCl with tracer amount of I-
Perlman *et al.* (1941)

Time after dose (hr)	5 hr	25 hr	48 hr	96 hr	197 hr
Blood	1.00	1.00	1.00	1.00	1.00
Reproductive					
Testes	0.44	1.11	1.37		0.92
Other					
Adrenals	0.33	0.72	0.65	0.27	0.46
Brain		0.13	0.07	0.06	0.04
Kidney	1.45	1.09	1.28	1.53	0.83
Liver	0.44	0.53	0.38	0.45	0.01
Muscle (gastrocnemius)	0.19	0.13	0.13	0.19	0.15
Skin	0.66	0.52	0.53	0.68	0.53

Tables 2 Perchlorate Organ to Blood Ratios in Rats

Rats given 100 mg $KClO_4$ ip

Anbar *et al.* (1959)

Time after dose (hr)	0.5 hr	4.0 hr	9.5 hr
Blood	1.00	1.00	1.00
Thyroid	2.16	1.46	4.42
GI			
Salivary gland	1.35		2.35
Reproductive			
Ovaries		1.06	
Testes	0.26		3.84
Other			
Adrenal gland	0.79	0.54	1.16
Hypophysis		0.27	
Liver	0.72	0.78	1.23
Mammary gland		0.66	
Muscle	0.19	0.27	0.45
Spleen	0.40	0.45	1.42

Table 3 Perchlorate Organ to Blood Ratios in Rabbits

Rabbits given 100 mg $KClO_4$ ip

Anbar *et al.* (1959)

Time after dose (hr)	2.0 hr	12.0 hr
Blood	1.00	1.00
Thyroid	1.16	4.38
GI		
Salivary gland	0.52	0.59
Reproductive		
Ovaries		0.54
Testes	0.52	
Other		
Adrenal gland		0.32
Liver	0.33	0.38
Muscle	0.22	0.12
Spleen	0.39	0.33

Table 4 Perchlorate Organ to Blood Ratios

Rabbits given $NaClO_4$ by different routes

Durand (1938)			
Dose	iv 920 mg $NaClO_4$	im 800 mg $NaClO_4$	oral 2000 mg $NaClO_4$
Time after dose (hr)	0.33 hr	1.83 hr	2.17 hr
Blood	1.00	1.00	1.00
GI			
Intestines	1.00	25.53	19.25
Gastric Mucosa	4.89	444.33	51.05
Stomach	0.50		1.18
Reproductive			
Ovaries	5.86	377.67	
Testicles			0.90
Other			
Bile	4.07	51.33	3.56
Bones	0.78	2.00	2.03
Brain	0.65	3.80	0.72
Heart	0.26	3.33	1.89
Kidney	0.77	1.67	2.04
Liver	0.08	0.10	0.85
Lungs	0.56	0.83	1.98
Muscles	0.27	0.07	0.84
Spleen	3.91	44.33	4.18
Urine	8.96	272.20	34.67

Selection of Model Compartments

The compartments used in the perchlorate and iodide PBPK models included the thyroid, salivary glands, gastrointestinal tract, slowly perfused tissues, and rapidly perfused tissues. A schematic of the preliminary models is provided in Figure 1. The gut, salivary glands and thyroid compartments are each comprised of two compartments to describe non-linear uptake of the iodide or perchlorate anions. The blood compartment is also split to describe diffusion of the anions from plasma to RBCs and vise versa. It is the free anions in the plasma that are readily available for diffusion and active uptake into other tissues. Therefore, RBCs become an important reserve of iodide. Rall *et al.*, (1950) found an average RBC to plasma ratio for iodide of 0.67 ± 0.054, from 10 determinations using various invitro blood iodide concentrations. Uptake in the slowly and rapidly perfused tissues compartments is represented by passive diffusion

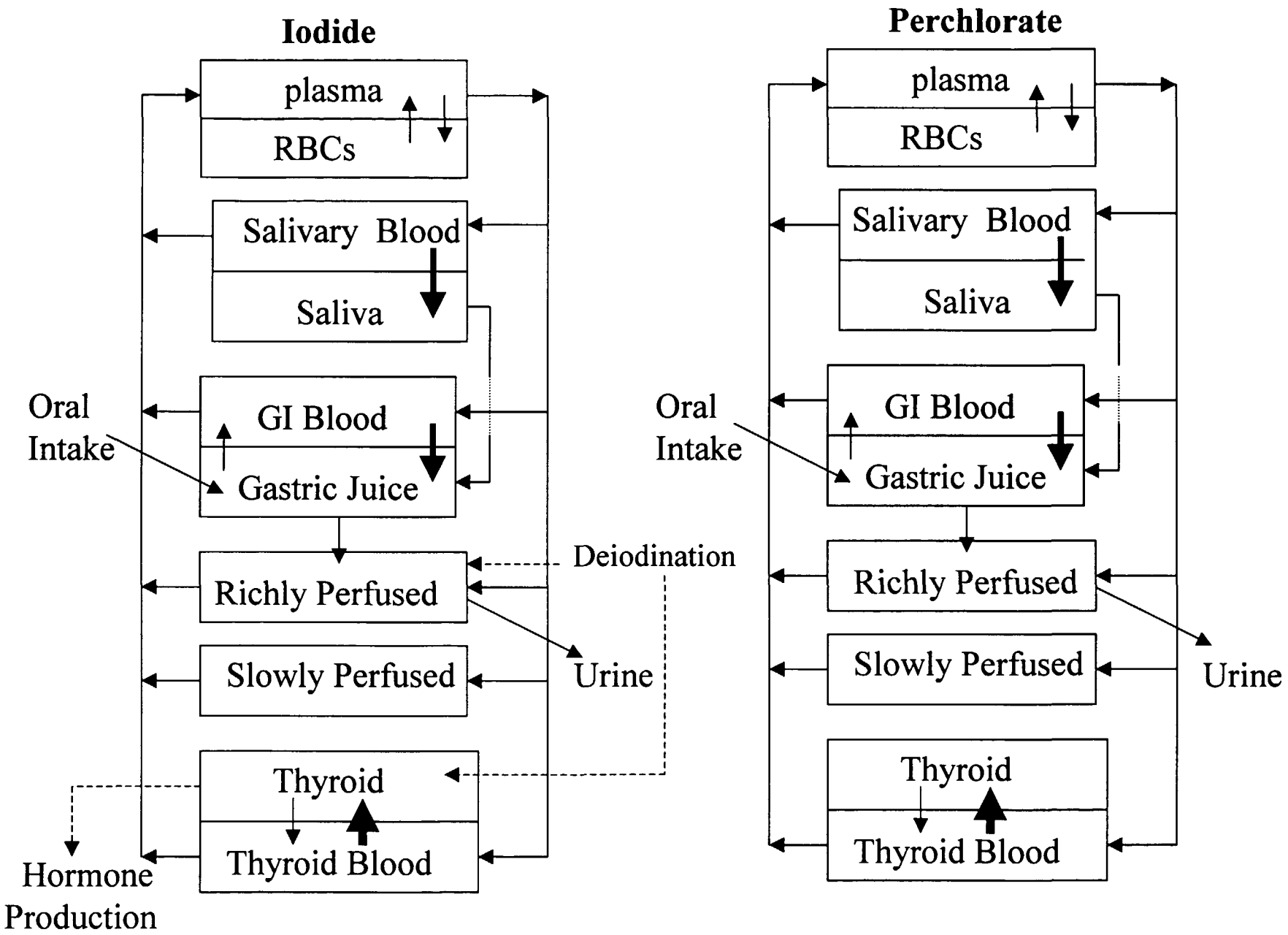


Figure 1. Flowchart of the separate perchlorate and iodide models.

Compartments of Active Uptake

Iodide is concentrated to the greatest extent in the thyroid. The ability of the thyroid gland to transport and concentrate iodide from blood is necessary for the synthesis of thyroid hormones. The key player in this process is the sodium-iodide symporter (NIS), an integral membrane protein that resides in the basolateral membrane of thyroid epithelial cells. Abnormalities in expression or function of the symporter can lead to thyroid disease.

The NIS simultaneously transports both Na^+ and I^- ions from extracellular fluid (i.e. plasma) into the thryoid epithelial cell. This process is an example of secondary active transport. Energy is provided by the electrochemical gradient of sodium across the cell membrane; the low intracellular concentration of sodium is maintained by sodium-potassium pumps (Ajjan *et al.*, 1998).

The NIS is most highly expressed in thyroid epithelial cells. Levels of expression can be detected in mammary gland, salivary glands, stomach and colon, but none of these tissues is known to organify iodide (Ajjan *et al.*, 1998; Spitzweg *et al.*, 1998). The presence of the symporter in mammary gland leads to secretion of iodine in milk, which is probably important for thyroid function in neonates. The most important stimulator of symporter gene and protein expression is thyroid-stimulating hormone, similar to what is observed with other important thyroid proteins such as thyroglobulin and thyroid peroxidase (Spitzweg *et al.*, 1998).

Active uptake in saliva and gastric mucosa is very important physiologically due to the quanity of these secretions. Several studies have reported higher iodide concentrations in the saliva than in gastric juice (Schiff *et al.*, 1947; Hays, 1964). However, gastric secretions account for the largest portion of the volume of iodide distribution. In gastric juice, iodide can reach concentrations up to 15 times that in plasma (Schiff *et al.*, 1947). Davenport *et al.* (1943) injected dogs with sodium iodide and found that the iodide was recoverable, as such and that there was no detectable molecular iodine, or organic iodine detected in the gastric juice. The concentration of the iodide in the gastric juice was independent of the rate of secretion. The iodide secreted in gastric juice and saliva is not lost from the body as it is rapidly reabsorbed after passing into the small intestines. By delaying the passage of iodide to the kidneys, the gastric and salivary NIS mechanisms help conserve the body's iodide. No studies measuring perchlorate in saliva or gastric juice were located. It is expected that perchlorate concentrates in these secretions, but to a lesser extent.

Physiological Parameters (Blood Flow Rates and Tissue Volumes)

Resting blood flow in the salivary glands is comparable to that of other gastrointestinal organs (approximately 50 ml per min per 100 g of tissue). Blood flow to the salivary gland can increase tenfold in response to enhanced functional activity (secretion) (Granger *et al.*, 1985).

Stimulation of salivary flow would obviously influence the total volume secreted in a given period of time, so expressions of measurement, such as percent, are not particularly meaningful

unless the exact conditions under which the saliva was collected are described. Becks and Wainwright (1943) reported a mean "resting" salivary flow of 20 ml/hr from 235 men (used as a first order excretion constant in the model) and 19 ml/hr from 249 women. However, the range of flow was 1 to 111 ml/hr. The volume and blood flow of the gut tissue and gastric mucosa were taken from Brown *et al.*, 1997. Assumptions used in the human model are listed in Table 5.

Table 5 Human Physiological Parameters in Perchlorate/Iodide Models

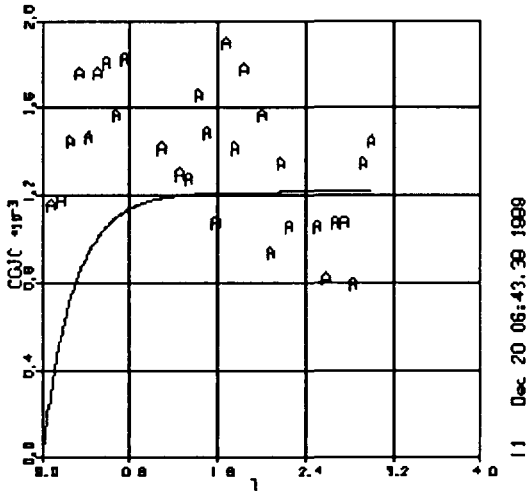
Parameter	Value	References
Body Weight	70 kg	
Blood Volume	0.068 x BW	Hays and Wegner, 1965
Plasma Volume	0.04 x BW	Hays and Wegner, 1965
RBCs Volume	0.028 x BW	Hays and Wegner, 1965
Thyroid Volume	0.000153 x BW	Berghout *et al.*, 1986
Gut Volume	0.02 x BW	Brown *et al.*, 1997
Salivary Gland Volume (parotid and submandibular)	0.015 x BW	Granger *et al.*, 1985
Thyroid Capillary Blood Volume	0.181 x Thyroid Vol.	Altman and Dittmer, 1971 (value derived from rats)
Gut Capillary Blood Volume	0.029 x Gut Vol.	Altman and Dittmer, 1971 (value derived from rats)
Slowly Perfused Volume	0.73 x BW	
Richly Perfused Volume	0.089 x BW	
Arterial Cardiac Output (QC)	15.87	Arms and Travis, 1988
Blood flow to thyroid	0.139 x QC	Brown *et al.*, 1997
Blood flow to Salivary Gland	0.008 x QC	Granger *et al.*, 1985
Blood flow to Gut	0.001 x QC	Brown *et al.*, 1997
Blood flow to Slowly Perfused	0.19 x QC	
Blood flow to Richly Perfused	0.66 x QC	

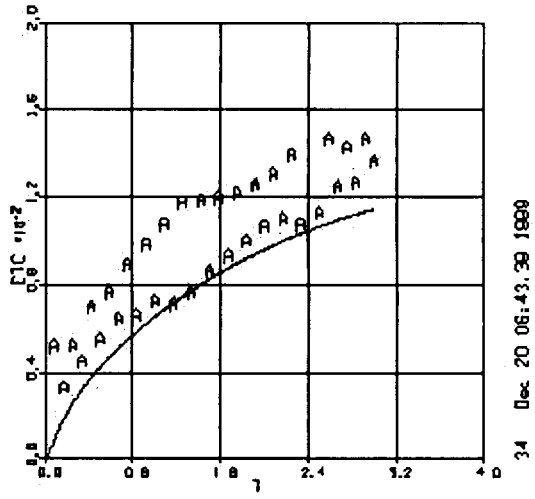
BW = Body weight of 70 kg
QC = arterial cardiac output (L/hr)

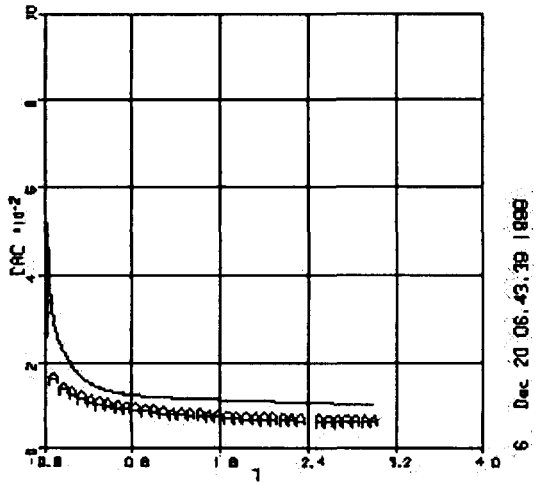
Iodide Affinity Constants

Affinity constants (Km) for tissues with active uptake of iodide were searched in the literature. For human, tissues only Km's derived from thyroid slices incubated with several medium iodide

concentrations were available. The mean Km value from thyroids of five normal individuals was $3.12 \pm 0.98 \times 10^{-5}$ M (Gluzman and Niepomniszcze, 1983). Values within this range were also used to represent the Km for active uptake in the gastric mucosa and saliva. Vmax values for each of those tissues were not located and therefore were derived by fitting the kinetic data. Affinity values for perchlorate in human tissues were not found in the literature. Illustrated below are preliminary model simulations vs actual iodide concentrations provided in Hays and Solomon (1965) for gastric juice (CGJC), cummulative urine (AUC), plasma (CAC) and thyroid (CTC).







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Spitzweg, C. and A.E. Heufelder. 1998. The sodium iodide symporter: its emerging relevance to clinical thyroidology. *Eur J Endocrinol* 138: 374-375.

Appendix II
Perchlorate Studies Used for Kinetics Data

Brabant G, P. Bergmann, C. M. Kirsch, J. Kohrle, R. D. Hesch, and A. von zur Muhlen. Early adaptation of thyrotropin and thyroglobulin secretion to experimentally decreased iodine supply in man. .Metabolism 41 (10):1093-1096, 1992

Five healthy males between 25 and 38 years were dosed as follows:

- 200 µg iodine supplement per day for four weeks
- 300 mg perchlorate, three times daily the following four weeks

Before dosing, normal thyroid function was measured for total and free thyroxine (T_4 and FT_4) and triiodothyronine (T_3 and FT_3) by determining thyroid-specific antibodies and TSH-receptor antibodies. At the end of the first four weeks of dosing with iodine, blood samples were taken every 10 minutes for 24 hours. The following day, intrathyroidal iodine content was determined using fluorescence scintigraphy. Beginning the next day subjects were treated with the perchlorate for four weeks to induce iodine depletion. Again blood was sampled every 10 minutes for the first 24 hours following the perchlorate dosing. T_3, T_4, FT_3, FT_4 and thyroxine-binding globulin (TBG) serum levels were measured as a mean of six serum samples obtained in six hour intervals by radioimmunoassay kits. Serum reverse T_3 and rT_3 concentrations were measured in the same serum samples. Thyroid globulin (Tg) serum levels were determined in 30-minute intervals, and in each 10 minute sample TSH was measured.

Perchlorate treatment significantly reduced intrathyroidal iodine concentration, but thyroid volume and total serum T_4, T_3, FT_3 and TBG were not altered. Mean 24-hour serum TSH levels, amount of TSH secreted/pulse, and FT_4 levels were significantly diminished, whereas Tg levels were significantly increased. This suggests a higher sensitivity of the thyroid to the effects of TSH under conditions of iodine depletion, allowing TSH to effectively release thyroid hormones and leading to a reduction of circulating serum TSH levels via negative feedback.

Note: The original data in the figures were requested from Dr. Brabant and received. The data in this study are relevant to early iodine deficiency; low level doses were used and ten-minute measurements were taken.

Burgi H., M. Benguerel, J. Knopp, H. Kohler, and H. Studer. Influence of perchlorate on the secretion on non-thyroxine iodine by the normal human thyroid gland. Eur J Clin Invest 4 (1):65-69, 1974

Two women and three men (healthy) were dosed as follows:

- Day 0 — oral administration of 80 µCi $Na^{125}I$
- Day 11 — injection - 30 µCi L-thyroxine ^{131}I
- Days 18-25 — oral administration of 200 mg 3 times/day of perchlorate
- Days 22-25 — oral administration of 15 mg 3 times/day carbimazole

Measurements:

- On day 13 (allowing two days for equilibrium after the administration of L-thyroxine ^{131}I), blood samples were drawn every one to two days up to day 25.
- Urine was collected every six to nine hours for total 48 hour samples from days 13-25.
- Thyroxine ^{131}I in blood was measured.
- Thyroidal secretions were calculated.

Under perchlorate administration, the non-thyroxine iodine secretion (secreted triiodothyronine and secreted endogenous iodide) increased significantly, suggesting that perchlorate discharges part, though not all, endogenous iodide.

Stanbury JB and JB Wyngaarden. Effect of perchlorate on the human thyroid gland. Metabolism 1:533-539, 1952

Three experiments were conducted on 12 patients with Graves' disease. In one, eight subjects received a blocking dose of 30 mg 1-methyl-2-mercaptoimidazole (MMI), an antithyroid drug, orally. A ninth patient received a dose of 200 mg propylthiouracil. Approximately one hour later a tracer of 10 μCi I^{131} was administered. At the first signal that radioidodine was accumulated in the gland (approximately 1 hr), an oral dose from 3 to 500 mg $KClO_4$ was administered. In a second group, two patients received 30 mg MMI (the blocking drug), and an hour later 100 mg $KClO_4$. Another hour later, the tracer was administered. In the third group (using three subjects) the blocking drug was omitted and the $KClO_4$ given before the tracer. Accumulation of iodide in the neck was recorded at frequent intervals up to 48 hours.

In the first group the counting rate dropped sharply within a few minutes of the $KClO_4$. With $KClO_4$.doses greater than 100 mg caused a fall in counting rates to or below the counting rates recorded in the thigh. Small doses resulted in an incomplete discharge of the I^{131}. Perchlorate was effective in the treatment of hyperthyroidism due to Graves' Disease at doses of 200 mg $KClO_4$, three times daily.

Dahlberg PA, A Bergmark, L Bjorck, A Bruce, L Hambraeus, and O Claesson. Intake of thiocyanate by way of milk and its possible effect on thyroid function. Am J Clin Nutr 39 (3):416-420, 1984.

Thirty seven subjects (28 females and nine males), between 16 and 54 years with normal health and no earlier incidence of goiter or thyroid dysfunction, were studied. Five were smokers. Smokers were studied separately as cigarettes are a source of thiocyanate from the enzymatic detoxification of cyanide by the enzyme thiosulfate sulfur transferase. Subjects received 12 weeks of 8 mg thiocyanate daily in milk.

Venous blood samples and urine samples were collected before the start of the experiment and after 4, 8 and 12 weeks. Measurements of thiocyanate and iodine in urine, and the serum concentrations of thyroid hormones (T_4, T_3, and TSH) were taken.

Thiocyanate increased significantly in serum and reached a maximum after four weeks. The increased serum levels coincided with an increased excretion in urine. Thyroxine, triiodothyronine, and TSH were all in normal range at the beginning and no significant changes were found during the experiment.

Martino E, S Mariotti, FA Lombardi, M Lenziardi, S Morabito, L Baschieri, A Pinchera, L Braverman, and M Safran. Short term administration of potassium perchlorate restores euthyroidism in amiodarone iodine-induced hypothyroidism. J Clin Endocrinol Metab 63 (5):1233-1236, 1986.

Prolonged treatment with amiodarone for various cardiac tachyarrhythmias may lead to hypothyroidism. Nine patients, who had been treated with amiodarone for 9 to 36 days, were subjects. The amiodarone was discontinued in all patients and three patients were followed for 80, 300 and 155 days, respectively without treatment, while five patients received 1.0 g $KClO_4$ daily for 9 to14 days and then were followed for an additional 60-228 days.

$KClO_4$ increased serum FT_4 values and decreased serum TSH concentrations within two weeks. Serum FT_4 and TSH concentrations changed very little in the three patients who did not receive $KClO_4$. After withdrawal of $KClO_4$ hypothyroidism recurred in three of the six patients.

Note: Figures present time series serum FT_4 and TSH concentrations in a patient who received the $KClO_4$ treatment and one who had not.

Martino E, F Lombardi, S Mariotti, M Lenziardi, L Baschieri, L Braverman, and A Pinchera. Treatment of amiodarone associated thyrotoxicosis by simultaneous administration of potassium perchlorate and methimazole. J Endocrinol Invest 9 (3):201-207, 1986.

Eight patients with amiodarone induced hyperthyroidism were treated with 40 mg methimazole and 1 gm $KClO_4$ daily. Blood levels and urine were monitored. The combined treatment resulted in a rapid fall of serum FT_4 and FT_3 into the normal range and the restoration of clinical euthyroidism within 16 to 36 days after therapy was started. Urinary iodine excretion progressively decreased in all patients receiving combined drug therapy.

Note: This study did not indicate if urine collected was total. Figures are very small and measurements are indicated over days and months. Original data should be requested.

Lucke G, R Hehrmann, K von Mayersbach, and A von zur Muhlen. Studies on circadian variations of plasma TSH, thyroxine and triiodothyronine in man. Acta Endocrinologica 86:81-88, 1977.

This study did not involve the dosing of human subjects with ClO_4^-, but evaluated circadian variation in thyroid hormones and TSH in the blood of five healthy male volunteers, ages 22 to 27 years. Blood was drawn every 20 min for 24 hours in four subjects and for 14 hours in

another (study was terminated at 14 hours because of a local phlebitis close to the area of venipuncture developed). Hormones were measured by sensitive radioimmmunoassays.

TSH demonstrated a diurnal pattern with peaks from 8 p.m. to 2 a.m. T_4 showed peak values from 8 to 12 a.m. and lowest from 11 p.m. to 3 a.m. T_3 levels were highest from 7 a.m. to 1 p.m. and lowest from 11 p.m. to 3 a.m. These patterns could not be demonstrated in all cases, but fluctuations were minor.

Durand J. Recherches sur l'elimination des perchlorates, sur leur repartition dans les organes et sur leur toxicite. Bull Soc Chim Biol 20:423-433, 1938.

Three men each ingested 0.784 g $NaClO_4$ dissolved in 100 g H_2O. Urinary and blood concentrations of $NaClO_4$ were monitored over the next 48 hours. Perchlorate ion diffused rapidly and was detected in the urine approximately 10 minutes after ingestion. Almost the entire amount of perchlorate administered was eliminated within 48 hours. There was no reduction of perchlorate to chlorate in the blood and an absence of methehemoglobulin.

Eichler O. Zur Pharmakologie der Perchloratwirkung [The pharmacology of the perchlorate effect]. Naunyn-Schmiedeberg's Arch Exp Path u Pharmak 144:251-260, 1929.

This paper primarily describes a technique for measuring and analyzing perchlorate in urine; however time course data on urinary excretion of perchlorate was provided for two subjects. Subject 1 received 2000 mg $KClO_4$; total $KClO_4$ recovered per day was measured over four days following dosage. Subject 2 received 2000 mg $KClO_4$; excretion was studied during the first 12 hours after dosage. In both cases approximately 94% of dose was excreted in the urine analyzed.

Nolte W, R Muller, H Siggelkow, D Emrich, and M Hufner. Prophylactic application of thyrostatic drugs during excessive iodine exposure in euthyroid patients with thyroid autonomy: a randomized study. Eur J Endocrinol 134 (3):337-341, 1996.

Patients from an iodine deficient area of Germany were screened for TSH. Inclusion criteria included normal FT_3 and FT_4 indices, delta-TSH < 3.5 μU/ml and a ^{99m}Tc uptake of more than 1.1% (to exclude patients with concurrent iodine contamination). Of those determined euthyroid, three groups of 17 people were treated. One group received 20 mg/day of thiamazole, another group received 900 mg/day $NaClO_4$, and a third group served as controls, receiving no treatments. Treatments were continued for 14 days.

At the end of 30 days from the initiation of treatment, mean FT4, T_4, T_3, FT_3, TSH and delta-TSH in blood and urine iodine excretion were derived from each group. Note: Time series data was not presented; only the mean of the parameters measured from 17 people, before and 30 days after the treatments are described.

Reichert L and H de Rooy. Treatment of amiodarone induced hyperthyroidism with potassium perchlorate and methimazole during amiodarone treatment. BMJ 298 (6687):1547-1548, 1989.

Three patients with amiodarone induced hyperthyroidism, ages 59 (case 1), 71 (case 2) and 67 (case 3), were given simultaneously 1 g/day $KClO_4$ for 40 days and methimazole at a starting dose of 40 mg/day while they continued to take amiodarone. The hyperthyroidism was diagnosed from a decreased TSH concentration and a highly raised FT_3 concentration. The FT_3 returned to normal values after two weeks in case 3 and after five weeks in cases 1 and 2.

Notes: Perchlorate was administered simultaneously with methimazol and amiodarone. TSH (mU/l), FT_4 (pmol/l) and FT_3 were measured over weeks, which did not provide good time-course data.

Zechmann W *et al.*, 1975. Absorption and Pharmacokinetics of large doses of 1-thyroxine in man. Wiener Klinische Wochenschrift. 87(22):751-5.

Absorption of T_4 from the GI tract and its metabolism were studied in euthyroid patients. Patients were given 250, 500, 1000 or 2500 ug T_4, mixed with 250 uCi ^{131}I-thyroxine. After thyroids had been blocked with $KClO_4$, the excretion was followed in feaces and urine for 4 to 5 days; the thyroid uptake of $^{131}I^-$ was measured and serial blood samples taken for T_4,

Note: There are time series data on feces and cumulative urine measurements from the different doses given after 96h. Changes in plasma concentrations of T_4, T_3, and TSH are given at one point after administration of the different T_4 doses.

Other Studies that contain Validation Information, but do not include Time Course Hormone Measurements.

Stewart R and I Murray. Effect of small doses of carrier iodide upon the organic binding of radioactive iodine by the human thyroid gland. J Clin Endocrinol Metab 27:500-508, 1967.

Perchlorate discharge tests (giving 400 mg $KClO_4$ orally 63 minutes after an IV injection of $^{131}I^-$) were carried out on individuals with normal and abnormal thyroid function. The amount of carrier iodine, which consisted of a known amount of $^{127}I^-$ mixed with $^{131}I^-$, given to the subjects varied from 100 to 2000 ug. After 45 minutes, blood samples were taken and serum $^{131}I^-$ measured. Serum $^{127}I^-$ concentrations were calculated from the $^{131}I^-$ concentrations. In addition thyroid $^{131}I^-$ was measured at that point in time.

Of 123 subjects, 40 were normal, 10 had received 10 U TSH 24 hours previously, 23 had simple nontoxic goiter, 4 had auto-immune thyroiditis, 24 were untreated thyrotoxic subjects, 21 were euthyroid patients who were treated for thyrotoxicosis (17 after radioactive iodine therapy and 4 after subtotal thyroidectomy).

Of the normal subjects, three who had been given 2000 μg $^{127}I^-$ (carrier iodide) all showed a fall in thyroid radioactivity after taking potassium perchlorate, as did 11 of 18 given 750 to 1500 μg. The discharge test was negative below the 500 μg $^{127}I^-$ dose and in those who had no $^{127}I^-$.

Note: Study does not provide time-course data, but it does provide thyroid iodide uptake and serum iodide concentrations after perchlorate dosing.

Morgans M and W Trotter. Defective organic binding of iodine by the thyroid in Hashimoto's thyroiditis. Lancet 1:553-555, 1957.

Twelve patients with Hashimoto's thyroiditis and 26 cases of simple goiter were studied. The simple goiter included both those with diffuse and those with nodular glands, thyroid function being normal in all 26 cases. Five hours after their last meal 20 to 40 uCi doses of $^{131}I^-$ were given by mouth, and counts were made simultaneously over thyroid and thigh regions 50 and 60 minutes after the dose. After the 60 minute count, patients drank a solution of 200 or 400 mg $KClO_4$ with 25 or 50 ml water, respectively. Neck and thigh counts were then measured at 10, 20, 30 and 40 minutes after receiving $KClO_4$.

Note: Retained iodine were measured by radioactivity. Volumetric values were not provided.

Fisher D. 1990. Euthyroid Low Thyroxine (T_4) and Triiodothyronine (T_3) States in Prematures and Sick Neonates. Pediatr Clin of North Am 37(6):1297-1312.

This paper was a good reference regarding normal thyroid growth. Human fetal cord serum total (T_4), free T_4 and TSH concentrations are plotted versus gestation age in weeks (from 11 to 40 weeks). Serum concentrations of T_4, T_3, rT_3 and TSH in premature infants were plotted versus days (the first 21 days of life).

Floyd J, W Beierwaltes, V Dodson, and E Carr. Defective iodination of tyrosine a cause of nodular goiter? J Clin Endocrinol Metab. 20:881-888, 1960.

A control group of 15 euthyroid, non-goitrous patients were used in this study. No one in the control group had a family history of thyroid disease. One gram of potassium thiocyanate (KSCN) was given orally to fasting patients two hours after an oral dose of 10-30 uC of $^{131}I^-$. Thyroidal $^{131}I^-$ uptake measurements were made with a scintilation detector over the neck at 0.5 and 1.0 hour after administration of KSCN.